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Original Article

Boron neutron capture therapy for locally recurrent head and neck squamous cell carcinoma: An analysis of dose response and survival

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ABSTRACT

Background and purpose: Head and neck squamous cell carcinoma (HNSCC) that recurs locally is a therapeutic challenge. We investigated the efficacy of boron neutron capture therapy (BNCT) in the treatment of such patients and the factors associated with treatment response and survival.

Methods and materials: Seventy-nine patients with inoperable, locally recurred HNSCC were treated with L-boronophenylalanine-mediated BNCT in Espoo, Finland, between February, 2003 and January, 2012. Prior treatments consisted of surgery and conventionally fractionated radiotherapy to a median cumulative dose of 66 Gy (interquartile range [IQR], 59–70 Gy) administered with or without concomitant chemotherapy. Tumor response was assessed using the RECISTv.1.0 criteria.

Results: Forty patients received BNCT once (on 1 day), and 39 twice. The median time between the 2 treatments was 6 weeks. Forty-seven (68%; 95% confidence interval [CI], 57–79%) of the 69 evaluable patients responded; 25 (36%) had a complete response, 22 (32%) a partial response, 17 (25%) a stable disease lasting for a median of 4.2 months, and 5 (7%) progressed. The patients treated with BNCT twice responded more often than those treated once. The median follow-up time after BNCT was 7.8 years. The 2-year locoregional progression-free survival rate was 38% and the overall survival rate 21%. A high minimum tumor dose and a small volume were independently associated with long survival in a multivariable analysis.

Conclusions: Most patients responded to BNCT. A high minimum tumor dose from BNCT was predictive for response and survival.

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Head and neck squamous cell carcinoma (HNSCC) can be cured with surgery and radiotherapy with or without systemic therapy, but locoregional recurrence is not uncommon. Cancers that recur locally are often considered inoperable, and may pose a therapeutic challenge, because reirradiation is often associated with substantial toxicity, and chemotherapy and immunotherapy have limited efficacy in most patients [1,2]. Intensity modulated radiotherapy (IMRT) and stereotactic radiotherapy (SRT) may allow delivery of relatively high re-treatment radiation doses without excessive adverse effects to the normal tissues and may improve tumor local control rates in selected patients [3–10]. Young age, a good performance status, a small gross tumor volume (GTV), histology other than squamous cell carcinoma, nasopharyngeal, oropharyngeal or laryngeal cancer location, and longer than a 2-year time interval between the first and the second radiotherapy courses are associated with favorable outcome after reirradiation [6,8–10]. Yet, prognosis of patients with recurrent HNSCC remains poor, and novel effective treatments are needed [8–9,11].

Boron neutron capture therapy (BNCT) is based on targeted release of high-linear energy transfer (high-LET) particles within cancerous tissue following boron (^{10}B) neutron capture. In practice, a boron carrier compound (for example, L-boronophenylalanine [L-BPA]) is first infused into a peripheral vein, usually resulting in a higher uptake of the ^{10}B carrier in cancerous tissues as compared with the normal tissues. The tumor is subsequently irradiated with an external neutron beam with energy in the epithermal range (0.5 eV < E < 10 keV), which leads to thermalization of the neutrons in tissue, boron neutron capture, and fission of ^{10}B to α-particles and lithium-7 nuclei. Because ^{4}He and ^{7}Li have a high-LET and a short range (<10 μm) in tissue, most of the absorbed dose is deposited in cancer [12]. Therefore, a high dose gradient may be achieved between cancerous and adjacent normal tissues provided

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that the boron carrier is selectively taken up by the tumor. Since BNCT is a high-LET radiotherapy modality, it is often delivered in a single fraction [13].

The relationships between the dose resulting from BNCT, tumor response to BNCT, and survival are incompletely understood. The maximum dose delivered from BNCT is usually limited by the tolerance of the adjacent critical tissues, particularly the oral and pharyngeal mucosa when treating patients with HNSCC, whereas the spinal cord is seldom the primary limiting radiosensitive organ. The tumor and normal tissue doses are usually estimated based on an average blood boron concentration at the time of neutron irradiation assuming a constant tumor-to-the whole blood boron concentration ratio [13,14]. In the present study we examined the relationships between the estimated tumor dose from BNCT, tumor volume, and treatment outcomes in a patient cohort with inoperable locally recurrent HNSCC. To our knowledge, this is the first study to investigate these relationships in this patient population.

Materials and methods

Patient and tumor characteristics

Seventy-nine patients with HNSCC, who were treated with BNCT at the FiR1 BNCT facility located in Espoo, Finland, between February, 2003 and January, 2012, were included in the study out of the total of 117 patients treated at this facility during this time period. The study participants were required to have histologically verified HNSCC that had recurred locally and was considered inoperable. We excluded patients with overt distant metastases, patients who had the target tumor partly resected, and those who interrupted neutron irradiation (Fig. 1).

Most patients (n = 75, 95%) had previously received radiotherapy to the tumor site (Table 1). The most common sites of tumor origin were the oral cavity and the pharynx. None of the patients received any other cancer treatment concomitantly with BNCT. When cancer progressed after BNCT, 23 patients received systemic chemotherapy, 4 received radiotherapy to the primary tumor site or a metastatic site, 7 underwent surgery, and 1 received gene therapy. An institutional ethics board approved the study (HUS/239/2017).

Treatment administration

L-BPA was complexed with fructose to form L-BPA-fructose (L-BPA-F) to increase solubility, and 350–400 mg/kg of L-BPA-F

Table 1
Characteristics of patients and tumors, and treatments given.

Characteristic	No. of patients (%) N = 79	Median (IQR)
Age (y)		62 (54, 68)
Gender		
Male	49 (62)	
Female	30 (38)	
Tumor site		
Larynx	8 (10)	
Maxillary sinus or paranasal cavity	8 (10)	
Pharynx	22 (28)	
Oral cavity	39 (49)	
Neck	2 (3)	
Primary treatment[*]		
Surgery	56 (71)	
Radiotherapy	75 (95)	
Chemotherapy	43 (54)	
No. of prior radiotherapy treatments		
0	3 (4)	
1	65 (82)	
2	10 (13)	
Unknown[†]	1 (1)	
Cumulative target radiotherapy dose from conventional radiotherapy		66 (59, 70)
Time from previous radiotherapy to BNCT (y)		1.1 (0.5, 2.4)
Gross tumor volume at the time of BNCT (cm^3)		105 (53, 187)
Tumor site at the time of BNCT		
Upper esophagus	1 (1%)	
Larynx	8 (10%)	
Maxillary sinus or paranasal cavity	9 (11%)	
Neck	7 (9)	
Oral cavity	33 (42)	
Pharynx	21 (27)	

Abbreviations: IQR = interquartile range; BNCT = boron neutron capture therapy.
[*] 1 patient may have received more than 1 type of treatment.

was then administered intravenously at a concentration of 30 g/L over a period of about 2 h before neutron irradiation at FiR 1, a 250-kW Triga Mark II nuclear research reactor (General Atomics, San Diego, CA) [16–18]. Neutron irradiation was usually given from 2 portals (range, 1–3). Irradiation was started when the blood boron concentration was approximately 20 µg/g, which occurred 79–104 (interquartile range, IQR) minutes after the end of L-BPA-F infusion. Neutron irradiation lasted for a median of 42 minutes. At the time of the first neutron field the median average blood boron concentration, measured with inductively coupled plasma atomic emission spectrometry [16], was 18 µg/g (IQR, 16–20 µg/g).
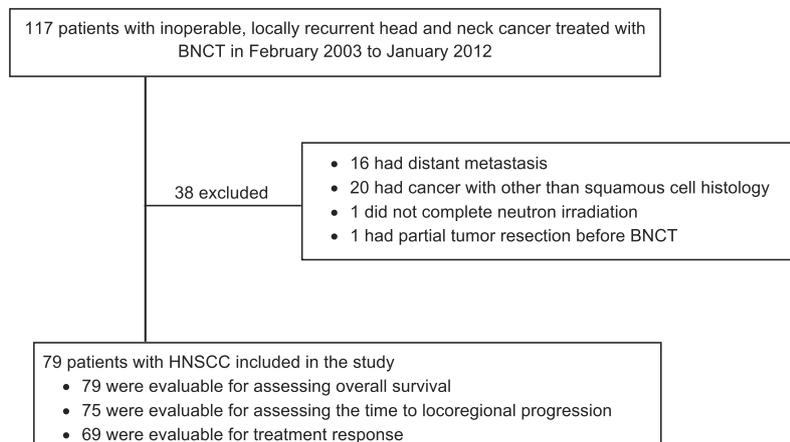

117 patients with inoperable, locally recurrent head and neck cancer treated with BNCT in February 2003 to January 2012

38 excluded
- 16 had distant metastasis
- 20 had cancer with other than squamous cell histology
- 1 did not complete neutron irradiation
- 1 had partial tumor resection before BNCT

79 patients with HNSCC included in the study
- 79 were evaluable for assessing overall survival
- 75 were evaluable for assessing the time to locoregional progression
- 69 were evaluable for treatment response

Fig. 1. Patient accrual to the study. BNCT = boron neutron capture therapy; HNSCC = head and neck squamous cell carcinoma.

Response evaluation

The patients were followed up at 4-week to 12-week intervals after BNCT. Clinical examination including pharyngolaryngoscopy and medical imaging (magnetic resonance imaging [MRI], computed tomography [CT], and/or positron emission tomography [PET]) were used to detect cancer recurrence, and either CT, MRI, or both were used to assess the tumor response. Treatment response was evaluated according to the RECISTv.1.0 criteria [15]. The minimum duration of stabile disease (SD) was defined as 2 months as calculated from the date of the first BNCT to the date of cancer progression.

Dose calculation

Treatment planning and the Monte Carlo computation-based dose calculation were performed with the software package SERA (Simulation Environment for Radiotherapy Applications; Idaho National Laboratory, Idaho Falls, ID) [17–19]. Four radiation dose components were calculated: (1) the boron dose, the high-LET dose resulting from the $^{10}B(n,\alpha)^7Li$ reaction; (2) the nitrogen dose from protons released in the thermal neutron capture reaction $^{14}N(n, p)^{14}C$ in tissue; (3) the photon dose from the thermal neutron capture reaction of hydrogen $^1H(n,\gamma)$ in tissue and the minor photon contamination in the neutron beam, and (4) the fast neutron dose caused by protons released from the hydrogen recoil reaction $^1H(n, n')p$ in tissue. The biological dose was derived as a sum of each dose component multiplied with a constant weighting factor, based on their relative biological effectiveness (RBE), except for the boron dose, which was multiplied with a boron carrier-specific compound effectiveness (CBE) factor [20]. The applied weighting factors were 3.2 for the nitrogen dose and the fast neutron dose, and 1.0 for the photon dose. For the boron dose, we applied tissue-specific weighting factors, 3.8 for the tumor, 2.5 for the mucosal membranes, 2.5 for the skin, and 1.3 for the central nervous system [13,22]. Tumor ^{18}F-fluoro-L-BPA accumulation was assessed prior to BNCT in 25 (32%) patients using PET yielding a median tumor-to-background standardized uptake value (SUV) of 3.3. ^{18}F-fluoro-L-BPA uptake results were not used in dose calculations. When biological doses are reported, the annotation "(W)" is added after the dose for clarity.

The boron concentration in the tumor was estimated to be 3.5 times higher than in the whole blood during neutron irradiation, and in the mucosal membranes 2 times higher. The mucosal membranes have relatively high BPA uptake and are radiation sensitive [13,21]. We limited the mucosal membrane absorbed physical dose to ≤6 Gy for each BNCT treatment.

Statistical analysis

Freedom from locoregional progression was defined as the time from the date of the first BNCT to the date of detection of cancer progression locoregionally. Patients who were alive without local progression were censored on the date of the last contact, and the patients who died without locoregional cancer progression on the date of death. Overall survival (OS) was computed from the date of the first BNCT to the date of death, censoring patients who were lost to follow-up and those alive on last date of contact.

Binary logistic regression was used to identify factors that are associated with achieving CR after BNCT (tested CR vs. PR, SD, or progressive disease). Non-normal distributions between groups were compared with the Mann–Whitney test or the Kruskal–Wallis test. Frequency tables were analyzed with the chi-squared test. Survival was analyzed using the Kaplan–Meier method, and survival between groups was compared with the log-rank test. A Cox proportional hazard regression model was used to identify covariables that are independently associated with survival. Hazard ratios (HR) and their confidence intervals (CI) were calculated with a univariable Cox model. All *p* values are 2-sided. Statistical analyses were performed with an SPSS Statistics version 1.0.0.580 (IBM Corp., Armonk, NY).

Results

Doses delivered

Forty (51%) of the 79 patients were treated with BNCT twice and 39 (49%) once. The patients were scheduled for 2 treatments except for the first patient in the series. The second BNCT was not given to the 38 remaining patients, because 7 had distant metastases detected, the neutron source was not available (*n* = 5), 5 died early, 5 had prolonged toxicity from the first BNCT, 3 had poor performance status, 3 refused further treatment, 2 were lost to follow-up, 2 had infection, 1 had an allergic reaction during the BPA infusion, 1 kidney failure, and 1 cancer progression. The reason for cancelation of the second BNCT was not reported in 3 cases.

The median time interval between the 2 treatments was 6 weeks (IQR, 5–8 weeks). Eighteen patients had the second BNCT delayed >6 weeks (mucosal toxicity, 12; poor performance status, 4; infection, 2). The median minimum GTV dose from the first BNCT was 15 Gy (W) (IQR, 12–18 Gy [W]). For the 40 patients who received only 1 BNCT, the median minimum tumor dose was 14 Gy (W) (IQR, 10–16 Gy [W]), and in the subset of 39 patients who received 2 BNCT treatments, the median of the sum of the minimum tumor doses from each treatment was 30 Gy (W) (IQR, 26–34 Gy [W]). The median of the maximum physical mucosa doses from single BNCT was 5.4 Gy (IQR, 4.9–5.9 Gy), corresponding to a biological dose of 11.9 Gy (W) (IQR, 10.5–12.9 Gy [W]). An average of 92% of the biological tumor dose resulted from the boron dose, 4% from the photon dose, 3% from the nitrogen dose, and 1% from the fast neutron dose.

Response to BNCT

Ten (13%) patients were not evaluable for response (8 died within 2 months from date of BNCT, 2 were lost to follow-up; Table 2). SD lasted for a median of 4.2 months (range, 2.2–19.2 months). The objective response rate (a CR or a PR) was 68% (47/69 patients; 95% CI, 57–79%; Fig. 2; Supplementary Fig. 1).

The evaluable patients treated twice with BNCT responded more often than the patients treated once (29/37 [78%] vs. 18/32

Table 2
Response to BNCT.

	CR (n, %)	PR (n, %)	SD (n, %)	PD (n, %)
All evaluable patients, *n* = 69[*]	25 (36%)	22 (32%)	17 (25%)	5 (7%)
BNCT given once, *n* = 31	6 (19%)	11 (36%)	10 (32%)	4 (13%)
BNCT given twice, *n* = 38	19 (50%)	11 (29%)	7 (18%)	1 (3%)

Abbreviation: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; BNCT = boron neutron capture therapy.
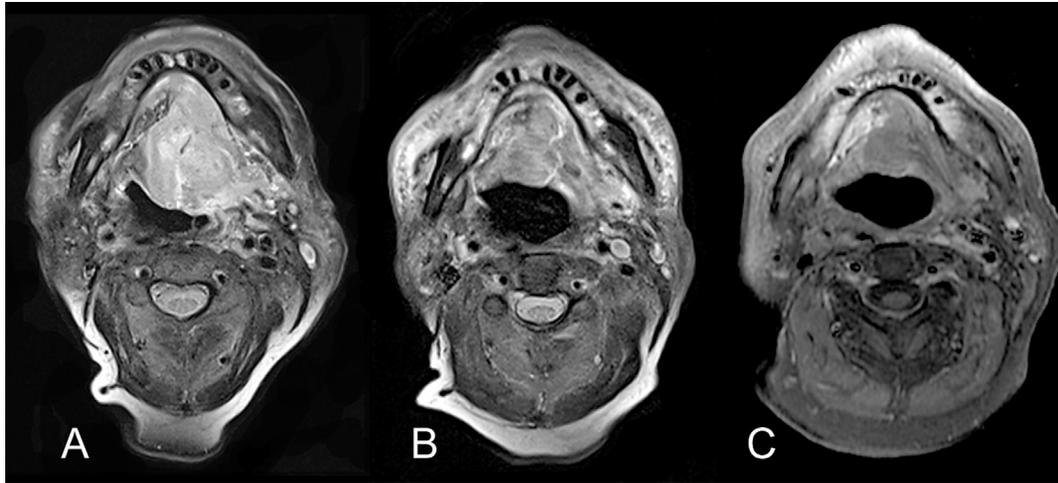* 10 patients in the series were not evaluable for response.

Fig 2. A 62-year-old woman with a local recurrence of tongue cancer growing into the floor of the mount after surgery and radiotherapy. An MRI prior to BNCT (A), 3 months after BNCT (B), and 2 years after BNCT showing a complete response (C).

[56%], respectively; *p* = 0.049). A high minimum tumor dose from the first BNCT was predictive for achieving CR (*p* = 0.038). Patients who achieved CR had a median minimum tumor dose of 17 Gy (W) from the first BNCT treatment as compared with 14 Gy (W) among the rest of the patients (*p* < 0.001). The GTV of the patients who achieved CR was smaller than the GTV in the rest of the evaluable
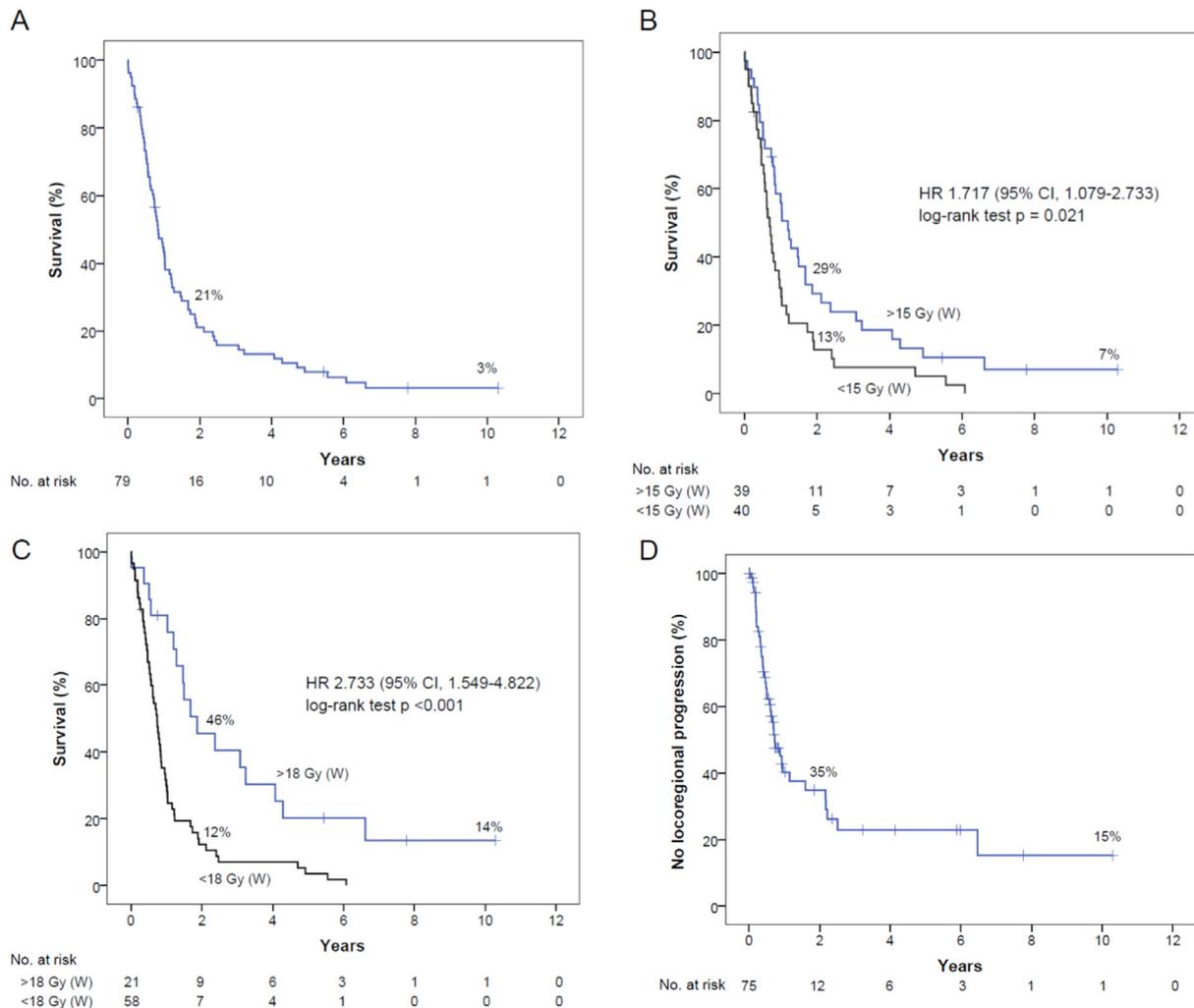

Fig. 3. Overall survival (A), overall survival in the subgroups of patients who received a minimum GTV dose of ≤15 Gy (W) or >15 Gy (W) (more than the median; B), overall survival in the subgroups of patients who received a minimum GTV dose of ≤18 Gy (W) or >18 Gy (W) (the highest quartile; C), and (D) freedom from locoregional progression. The censored patients are indicated with a bar. The 2-year and 10-year survival rates are shown.

Table 3
Multivariable Cox regression hazard model for overall survival.

Covariable[*]	Hazard ratio (95% CI)	p
Gross tumor volume (cm^3)	1.003 (1.001–1.005)	0.007
Minimum dose from the first BNCT (Gy [W])	0.941 (0.891–0.994)	0.030
Time from prior photon irradiation to the date of BNCT (years)	1.030 (0.934–1.136)	0.557

Abbreviations: CI = Confidence interval; BNCT = boron neutron capture therapy.
[*] The covariables were entered as continuous factors into the model.

patients (median, 53 cm^3, 105 cm^3, and 143 cm^3, respectively; $p < 0.001$). Twenty-two (81%) of the 27 patients who had a GTV smaller than the median (<105 cm^3) and who received a minimum tumor dose higher than the median (>15 Gy [W]) responded (had CR or PR). Neither age at the time of BNCT (tested < median [62 years] vs. > median; $p = 0.680$) nor the length of the time interval from prior photon irradiation to the date of BNCT (median [≤1.1 years] vs. >median; $p = 0.097$) was associated with response.

Overall survival

Three patients were alive without head and neck cancer 5.5, 7.8, and 10.3 years after the date of BNCT. The median OS was 10 months, and 2-year OS was 21% (Fig. 3).

A GTV size smaller than the median (≤105 cm^3, $p = 0.001$), a minimum tumor dose higher than the median minimum tumor dose from the first BNCT (15 Gy [W], $p = 0.021$), a minimum tumor dose in the highest quartile (>18 Gy [W], $p < 0.001$), and a time longer than the median time (1.1 years) from prior photon radiotherapy to the date of BNCT ($p = 0.004$) were identified as factors associated with favorable OS in univariable survival analyses, whereas gender, age (tested ≤ median vs. >median), the primary tumor site, the number of BNCT treatments given (1 vs. 2), and the time between stopping L-BPA-F infusion and starting neutron irradiation (≤median [91 minutes] vs. >median) were not significantly associated with OS in univariable analyses ($p > 0.05$ for each analysis). The minimum tumor dose in the highest quartile (>18 Gy [W]) from the first BNCT had the strongest association with OS. Of the patients who received a dose >18 Gy (W), 46% survived for 2 years after BNCT as compared with 12% of those who received a smaller dose (Fig. 3, panel C).

Multivariable analysis of overall survival

To find out which of the factors examined were independently associated with OS, we entered the factors that were significantly associated with OS in a univariable analysis into a Cox multivariable model. A small GTV size and a high minimum tumor dose from the first BNCT were independently associated with OS, whereas the time interval between prior photon irradiation and the date of BNCT were not (Table 3). As a sensitivity analysis, we entered the number of BNCT treatments given (1 or 2) as the fourth covariable into the model, but the results remained essentially unaltered. When the minimum GTV dose resulting from the first BNCT treatment was replaced with the sum of the minimum GTV doses in those cases when 2 BNCT treatments were given as a covariable in the model, the GTV size was the only significant factor associated with survival (HR 1.003, 95% CI 1.001–1.005, $p = 0.001$).

Locoregional tumor control

The median time without locoregional cancer progression was 9 months, and 35% of the patients were free from locoregional pro-

gression 2 years after BNCT (Fig. 3). A GTV smaller than the median and a minimum tumor dose from the first BNCT in the highest quartile were significantly associated with freedom from locoregional progression in univariable survival analyses ($p = 0.032$ and 0.007, respectively). A minimum tumor dose from the first BNCT higher than the median tended to be associated with a long time to locoregional progression ($p = 0.095$), whereas age, gender, tumor site, and the number of BNCT treatments given were not ($p > 0.05$ for each analysis). When the tumor size and the minimum tumor dose from the first BNCT treatment were entered into a Cox multivariable model as continuous variables, a high minimum tumor dose from the first BNCT was significantly associated with a long time to locoregional progression (HR 0.911, 95% CI 0.842–0.986, $p = 0.021$), whereas tumor size was not ($p = 0.451$).

Discussion

We found that most (68%) patients with inoperable, locally recurrent, and previously irradiated HNSCC responded to BNCT, and the 2-year OS was 21%. Importantly, the data suggest that a high minimum dose delivered to the tumor from the first BNCT is a key predictive factor for absence of locoregional progression and OS, whereas the number of BNCT treatments given (either 1 or 2) may be a less important factor. To our knowledge, a similar study has not been conducted earlier, and the current patient cohort is the largest series with inoperable locally recurrent HNSCC treated with BNCT reported to date.

In an agreement with the present findings, tumor size and the radiation dose are also prognostic when patients with inoperable recurrent HNSCC are re-irradiated with photons [7,9]. Of note, most of the tumors we treated with BNCT were large (median GTV size, 105 cm^3) as compared with some series where recurrent HNSCC was treated with conventional radiotherapy using SRT or IMRT (median GTV size, 19–30 cm^3) [3,7,9], and where tumor size <25 cm^3 was identified a favorable prognostic factor for survival and achieving a CR [7,9]. In the present series, only 8/79 (10%) patients had tumor volume <25 cm^3. Interestingly, all 8 patients responded to BNCT (CR, 7; PR, 1), and had a median OS of 25 months.

The minimum GTV dose of ≥18 Gy (W) (the highest quartile dose) was associated with the best survival rates. This finding may be supported by the observations done with conventional photon irradiation using SRT. In one study [9] a dose >35 Gy delivered with SRT in 5 fractions to a small (<25 cm^3) volume was associated with favorable survival, which dose corresponds to a single fraction dose of ≥18 Gy as calculated with linear quadratic equation using $\alpha/\beta = 10$, but drawing firm conclusions is challenging due to the differences between the studies and the potential biases involved.

The current results appear to be in line with the results obtained by others when evaluating BNCT as a treatment for head and neck cancer, although the series differ and the data are scarce. In a study consisting of 62 patients with either newly diagnosed inoperable head and neck cancer or recurrent cancer the response rate to BNCT was 58%, median OS 10 months, and the 2-year OS rate 24% [23]. The median minimum tumor dose delivered was 17.9 Gy (W), the tumor volumes were not reported. In another series where 17 patients with recurrent inoperable head and neck carcinoma or sarcoma were treated with BNCT twice, 12 (71%) patients responded, 2-year OS was 47%, and the 2-year locoregional control rate 28%. In this study, the median tumor volume was 15.6 cm^3 and the minimum tumor dose from the first BNCT 13 Gy (W) [24].

The retrospective nature is a limitation of the current study. Therefore, the response evaluations and follow-up schedules were

done as per the institutional guidelines. The patient population may be considered representative, since we included all patients treated with BNCT in the center during the time period who fulfilled the study inclusion criteria. The tumors were not tested routinely for human papilloma virus infection, since this was not the norm at the time when the patients were treated, and, therefore, these data are not available to us. The adverse effects related to BNCT were not the topic of the present study, but, in general, they resemble those of conventional radiotherapy, the most common acute severe (grade 3) adverse effects consisting of oral mucositis, oral pain, and fatigue [17,18]. No treatment-related deaths were recorded.

The main disadvantages of BNCT have been insufficient dose to deep-seated targets and the dependency on nuclear reactors as the neutron source. The former limitation may be improved with novel ^{10}B carriers, and the latter with accelerator-based neutron sources that have recently become available for hospital installations [25,26]. BNCT might be applicable also as a booster treatment to conventional radiotherapy [27,28] or be combined with systemic cancer therapies. Randomized trials comparing BNCT with other radiotherapy modalities have not been carried out, but are needed for the positioning of BNCT in the treatment armamentarium of patients with head and neck cancer.

In summary, most patients with locally recurrent HNSCC respond to L-boronophenylalanine-mediated BNCT despite prior conventional radiotherapy in their history. A high minimum tumor dose from BNCT is associated with a high response rate, a longer time to locoregional progression after BNCT, and survival.

Funding

Declaration of Competing Interest

Hanna Koivunoro is employed by Neutron Therapeutics Inc., and has received financial compensation from Neutron Therapeutics Inc.

Heikki Joensuu has a co-appointment at Orion Pharma, has received consultation fees from Orion Pharma, is an advisor of Neutron Therapeutics Inc. and has received financial compensation from Neutron Therapeutics Inc, and has stock ownership in Sartar Therapeutics and Orion Pharma.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.04.033.

References

[1] Langer CJ, Harris J, Horwitz EM, et al. Phase II study of low-dose paclitaxel and cisplatin in combination with split-course concomitant twice-daily reirradiation in recurrent squamous cell carcinoma of the head and neck: results of Radiation Therapy Oncology Group Protocol 9911. J Clin Oncol 2007;25:4800–5.

[2] Spencer SA, Harris J, Wheeler RH, et al. Final report of RTOG 9610, a multi-institutional trial of reirradiation and chemotherapy for unresectable recurrent squamous cell carcinoma of the head and neck. Head Neck 2008;30:281–8.

[3] Voynov G, Heron DE, Burton S, et al. Frameless stereotactic radiosurgery for recurrent head and neck carcinoma. Technol J Cancer Res Treat 2006;5:529–35.

[4] Siddiqui F, Patel M, Khan M, et al. Stereotactic body radiation therapy for primary, recurrent, and metastatic tumors in the head-and-neck region. Int J Radiat Oncol Biol Phys 2009;74:1047–53.

[5] Roh KW, Jang JS, Kim MS, et al. Fractionated stereotactic radiotherapy as reirradiation for locally recurrent head and neck cancer. Int J Radiat Oncol Biol Phys 2009;74:1348–55.

[6] Unger KR, Lominska CE, Deeken JF, et al. Fractionated stereotactic radiosurgery for reirradiation of head-and-neck cancer. Int J Radiat Oncol Biol Phys 2010;77:1411–9.

[7] Rwigema JC, Heron DE, Ferris RL, et al. The impact of tumor volume and radiotherapy dose on outcome in previously irradiated recurrent squamous cell carcinoma of the head and neck treated with stereotactic body radiation therapy. Am J Clin Oncol 2011;34:372–9.

[8] Ohnleiter T, Truntzer P, Antoni D, et al. Prognostic factors for head and neck cancer reirradiation: a systematic review. Cancer Radiother 2017;21:316–38.

[9] Vargo JA, Ward MC, Caudell JJ, et al. A multi-institutional comparison of SBRT and IMRT for definitive reirradiation of recurrent or second primary head and neck cancer. Int J Radiat Oncol Biol Phys 2018;100:595–605.

[10] Velez MA, Veruttipong D, Wang PC, et al. Re-irradiation for recurrent and second primary cancers of the head and neck. Oral Oncol 2017;67:46–51.

[11] Ward MC, Riaz N, Caudell JJ, et al. Refining patient selection for reirradiation of head and neck squamous carcinoma in the IMRT era: a multi-institution cohort study by the MIRI collaborative. Int J Radiat Oncol Biol Phys 2018;100:586–94.

[12] Barth RF, Vicente MG, Harling OK, et al. Current status of boron neutron capture therapy of high grade gliomas and recurrent head and neck cancer. Radiat Oncol 2012;7:146.

[13] Coderre JA, Morris GM. Review: the radiation biology of boron neutron capture therapy. Rad Res 1999;151:1–18.

[14] González S, Santa Cruz G. The photon-isoeffective dose in boron neutron capture therapy. Radiat Res 2012;178:609–21.

[15] Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.

[16] Joensuu H, Kankaanranta L, Seppala T, et al. Boron neutron capture therapy of brain tumors: clinical trials at the Finnish facility using boronophenylalanine. J Neurooncol 2003;62:123–34.

[17] Kankaanranta L, Seppälä T, Koivunoro H, et al. Boron neutron capture therapy in the treatment of locally recurred head and neck cancer. Int J Radiat Oncol Biol Phys 2007;69:475–82.

[18] Kankaanranta L, Seppälä T, Koivunoro H, et al. Boron neutron capture therapy in the treatment of locally recurred head-and-neck cancer: final analysis of a phase I/II trial. Int J Radiat Oncol Biol Phys 2012;82:e67–75.

[19] Nigg DW. Computational dosimetry and treatment planning considerations for neutron capture therapy. J Neurooncol 2003;62:75–86.

[20] International Atomic Energy Agency, Current status of neutron capture therapy, IAEA-TECDOC-1223, 2001.

[21] Wittig A, Collette L, Appelman K, et al. EORTC trial 11001: Distribution of two 10B-compounds in patients with squamous cell carcinoma of head and neck, a translational research/phase 1 trial. J Cell Mol Med 2009;13:1653–65.

[22] Coderre JA, Chanana AD, Joel DD, et al. Biodistribution of boronophenylalanine in patients with glioblastoma multiforme: boron concentration correlates with tumor cellularity. Radiat Res 1998;149:163–70.

[23] Suzuki M, Kato I, Aihara T, et al. Boron neutron capture therapy outcomes for advanced or recurrent head and neck cancer. J Radiat Res 2014;55:146–53.

[24] Wang LW, Chen YW, Ho CY, et al. Fractionated boron neutron capture therapy in locally recurrent head and neck cancer: a prospective phase I/II trial. Int J Radiat Oncol Biol Phys 2016;95:396–403.

[25] Kreiner AJ, Bergueiro J, Cartelli D, et al. Present status of accelerator-based BNCT. Rep Pract Oncol Radiother 2016;21:95–101.

[26] Tanaka H, Sakurai Y, Suzuki M, et al. Experimental verification of beam characteristics for cyclotron-based epithermal neutron source (C-BENS). Appl Radiat Isot 2011;69:1642–5.

[27] Kankaanranta L, Saarilahti K, Mäkitie A, et al. Boron neutron capture therapy (BNCT) followed by intensity modulated chemoradiotherapy as primary treatment of large head and neck cancer with intracranial involvement. Radiother Oncol 2011;99:98–9.

[28] Yamamoto T, Nakai K, Kageji T, et al. Boron neutron capture therapy for newly diagnosed glioblastoma. Radiother Oncol 2009;91:80–4.